REMARKS

Claims 21, 22, 25, 26, 28, 29, 32, 33, 36, and 37 are pending. Claims 1-20, 23, 24, 27, 30, 31, 34, and 35 were previously canceled. Claims 25, 26, 32, and 33 are canceled herein without prejudice. Claims 21, 22, 28, 29, 36, and 37 are amended herein. New claims 38 and 39 are presented herein. Accordingly, amended claims 21, 22, 28, 29, 36, and 37, and new claims 38 and 39 are presently under consideration.

Support for amendment to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claims 21, 22, 28, 29, 36, and 37 is found, for example, in paragraph 11, and Table 1 of the specification. Support for amendment to claims 21, 28, 36, and 37 is also found, for example, in paragraphs [27]-[28]. No issue of new matter is introduced by these amendments.

Support for new claims 38 and 39 is found throughout the specification and in the original claims. Specifically, support for new claim 38 is found, for example, in previously presented claims 21, 24, and 25, and, for example, in paragraph 11, and in Table 1 of the specification; in paragraph 20; in paragraph 69, wherein support for a suitable dose being an efficacious amount of material is found; in paragraphs 29 and 30, wherein support for glucosylceramide synthase as an example of an enzyme responsible for glucosylceramide synthesis is presented; and in paragraphs [27]-[28]. No issue of new matter is introduced by these amendments.

Objection to the Specification

The specification is objected to for allegedly failing to provide antecedent basis for the claimed subject matter. More specifically, the specification allegedly fails to provide literal antecedent basis for "mucopolysaccharide disease". The claims are amended herein to recite "mucopolysaccharidosis disease", rather than "mucopolysaccharide disease", so as to obviate this objection.

Rejections under 35 USC § 112

Claims 21, 25, 26, 28, 32, 33, 36, and 37 are rejected under 35 USC § 112, second paragraph, for alleged indefiniteness. Claims 21, 28, 36, and 37 are amended herein to clarify

the subject matter. In view of the amendments to the claims, this rejection, as it applied to claims 21, 25, 26, 28, 32, 33, 36, and 37 is obviated.

In view of the amendments to the claims, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 USC § 112, second paragraph.

Rejection Under 35 U.S.C. § 102

Claims 21, 22, 25, 28, 29, 32, 36, and 37 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Fan et al. (United States Pub No. 2002/0035072) or Meeker et al. (United States Pub No. 2002/0095135). Claims 25 and 32 are canceled herein, thereby obviating any rejection of these claims. In view of Applicant's arguments presented herein and amendments to the claims, the rejection as it applied to claims 21, 22, 25, 28, 29, 32, 36, and 37 is respectfully traversed.

Claims 21, 28, 36, and 37 are amended herein to specify that the inhibitor of glucosylceramide synthase administered to a patient afflicted with a mucopolysaccharidosis (MPS) disease is N-butyldeoxynojirimycin. Applicant asserts that Fan et al. do not teach a method of treating a patient afflicted with any MPS disease that calls for administering N-butyldeoxynojirimycin (NB-DNJ). This assertion is corroborated by the fact that Table 4, which provides a "summary of potent competitive inhibitors which are expected to effectively enhance the mutant enzyme activity associated with lysosomal storage disorders..." (see end of paragraph [0113]) does not indicate that NB-DNJ would be useful for treatment of any of the MPS diseases listed therein. Instead, Fan et al. have set forth a competitive inhibitor predicted to enhance the activity of the indicated mutant enzyme which is associated with each particular MPS disease listed therein. This approach is consistent with the chemical chaperone strategy described throughout the Fan et al. application and reiterated briefly below, whereby competitive inhibitors are selected to interact with the mutant enzyme causative of the particular disease.

In view of the above, Fan et al. fail to teach each of the elements of the instant claims. Accordingly, Applicant deferentially requests reconsideration and withdrawal of the rejection of the amended claims based on Fan et al.

More specifically, as described, for example, in the Abstract of United States Pub No. 2002/0035072, the disclosure of Fan et al. is directed to a method for enhancing in a mammalian cell the activity of an enzyme associated with a lysosomal storage disorder by administering a competitive inhibitor of the enzyme in an amount effective to enhance the activity of the enzyme. Preferred compounds for use in the method described therein are imino sugars and related compounds. Fan et al., therefore, teach a targeted method of competitive inhibition, wherein the mutant enzyme **associated with a particular lysosomal storage disease** is targeted for **specific** inhibition by a competitive inhibitor that associates with the mutant enzyme so as to induce a stable molecular conformation. In so doing, the chemical chaperone improves the stability of the mutant enzyme and improves enzymatic activity. This methodological approach is reiterated throughout the Fan et al. application. See, for example, paragraphs [0011], [0033], [0055], and [0111]-[0112]. Table 1 illustrates the underlying reasoning of the approach of Fan et al. and matches the lysosomal storage disorder with the causative defective enzyme(s) identified. In accordance with the teaching of Fan et al., therefore, a skilled practitioner would administer a competitive inhibitor to a patient suffering from a lysosomal storage disorder, wherein the competitive inhibitor is specifically selected for its ability to associate with and act as a chemical chaperone for the mutant enzyme causative of the lysosomal storage disorder.

Applicant's understanding of the chemical chaperone strategy of Fan et al. is corroborated by all three of the Examples presented in the published application. More specifically, the Examples presented therein are directed to Fabry disease, which is associated with mutant α-Galactosidase A (α-Gal A); G_{M1} gangliosidosis, which is associated with mutant acid β-galactosidase (β-Gal); and Gaucher disease, which is associated with mutant acid β-glucosidase (β-Glu) or glucocerebrosidase. In each Example, competitive inhibitors were selected based on their ability to inhibit and enhance (via stabilization) the activity of the mutant enzyme involved in the disorder. No Examples are provided demonstrating application of the chemical chaperone strategy to any mucopolysaccharidosis (MPS) disease.

The Examiner maintains that Fan et al. contemplates treating patients having various MPS diseases by administering imino sugar inhibitors of glucosylceramide synthase such as N-butyldeoxygalactonojirimycin. The Examiner directed Applicant's particular attention to Table 1, and paragraphs [0015], [0031]-[0032], [0073], and Table 2. As indicated above,

Table 1 correlates causative defective enzymes with lysosomal storage disorders and sets forth the logic underlying Fan et al.'s chemical chaperone strategy whereby competitive inhibitors are paired with defective enzymes involved in disease etiology. Paragraph [0015] refers to Table 1 and further supports Applicant's understanding of the chemical chaperone strategy whereby competitive inhibitors are selected to interact with the mutant enzyme causative of the particular disease. Paragraph [0031] refers broadly to dosing parameters and paragraph [0032] reinforces the concept of the chemical chaperone strategy. Paragraph [0073] describes N-butyldeoxygalactonojirimycin (NB-DGJ), but fails to suggest that this competitive inhibitor would have any utility as a competitive inhibitor for any MPS disorder. Table 2 is similarly silent with respect to a mutant enzyme that has been shown to be associated with any MPS disorder. Table 2 shows results pertaining to in vitro inhibition of α-Gal A by DGJ derivatives. It is noteworthy that defective α-Gal A is associated with Fabry disease, which is not an MPS disease.

In view of the above, Applicant respectfully asserts that Fan et al. do not teach treating patients having various MPS diseases by administering NB-DGJ. This is underscored by the fact that Table 4, which provides a "summary of potent competitive inhibitors which are expected to effectively enhance the mutant enzyme activity associated with lysosomal storage disorders..." (see end of paragraph [0113]) does not indicate that NB-DGJ would be useful for treatment of any of the MPS diseases listed therein. Instead, and in keeping with their chemical chaperone strategy whereby competitive inhibitors are selected to interact with the mutant enzyme causative of the particular disease, Fan et al. have set forth a competitive inhibitor predicted to enhance the activity of the indicated mutant. It is evident, therefore, that NB-DGJ is not envisioned as a suitable competitive inhibitor for any of the mutant enzymes shown to be associated with a MPS disease listed therein.

As indicated on the face of United States Pub No. 2002/0095135 (Meeker et al.), this application was filed June 19, 2001. The Meeker et al. application, in turn, claims priority from United States Provisional Application No. 60/212,377 filed June 19, 2000. A review of the specification filed in connection with 60/212,377, however, reveals that the Meeker et al. application is not entitled to the priority of this earlier filing for the alleged disclosure of the present invention. More specifically, United States Provisional Application No. 60/212,377 is directed to combination enzyme replacement and gene therapy for the treatment of

lysosomal storage diseases. See entire document and, more particularly, the Summary section, for example, beginning at page 6. There is no teaching relating to substrate inhibition for the treatment of lysosomal storage diseases in Provisional Application No. 60/212,377. Indeed, the disclosure relied upon by the Examiner was first made at the filing date of United States Pub No. 2002/0095135 (June 19, 2001). In that the present application is entitled to a priority date of January 12, 2001, by virtue of priority document U.K. Application No. 0100889.5, the Meeker et al. application fails to meet the criteria established for a prior art reference under 102(e) because it does not disclose the instant invention prior to Applicant's own invention of the same.

Even if Meeker et al. were properly cited as prior art under 102(e), a contention which Applicant asserts is not supported by the evidence, it is noteworthy that the Meeker et al. application (Pub No. 2002/0095135) is directed to combination therapy. A directive to combination therapy is evidenced throughout the specification. The Examiner's attention is respectfully directed to paragraphs [0041]-[0045], [0064], and [0066]-[0067], which attest to a combination therapy approach. The following passage (paragraph [0030]) excerpted from Meeker et al. also typifies this approach:

"This invention provides various combinations of enzyme replacement therapy, gene therapy, and small molecule therapy for the treatment of lysosomal storage diseases. According to the invention, several general approaches are provided. Each general approach involves ***combining at least two*** *of enzyme replacement therapy (ERT), gene therapy (GT), and small molecule therapy (SMT) in a manner which optimizes clinical benefit while minimizing disadvantages associated with using GT or ERT or SMT alone."* Emphasis added.

That being the case, Meeker et al. do not teach a therapeutic approach that calls for administration of only small molecule therapy (e.g., imino sugar inhibitors of glucosylceramide synthase) for the treatment of any lysosomal storage disease. Meeker et al. teach combination therapy. By extension, therefore, Meeker et al. also fail to teach a therapeutic approach directed to administration of only imino sugar inhibitors of glucosylceramide synthase for the treatment of mucopolysacccharidosis diseases.

In view of the above, United States Pub No. 2002/0095135 is not a *bona fide* prior art reference under 102(e) and thus, a rejection based on this reference is improper. The rejection, as it applied to claims 21, 22, 25, 28, 29, 32, 36, and 37, is therefore respectfully traversed. Reconsideration and withdrawal of the rejection are, therefore, deferentially requested.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 21, 22, 25, 28, 29, 32, 36, and 37 under 35 U.S.C. §102 and withdraw the rejection.

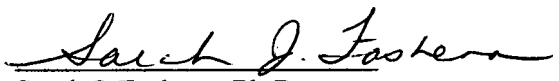
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Enclosures: Petition for a Three Month Extension of Time